CCR5: Window of Biocapitalism

The Genealogy of a Gene: Patents, HIV/AIDS, and Race

Author: Myles W. Jackson
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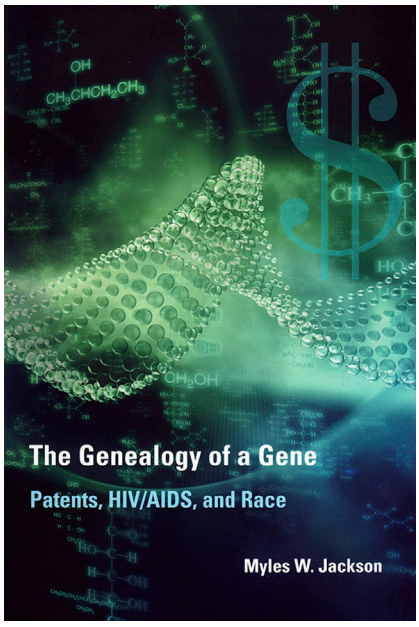
The author of *the Genealogy of a Gene*, Myles W. Jackson, uses the gene CCR5 as a window framing a vista of biocapitalism. With many compartmentalized panes, this window looks at different edges of its scene as the author retells the scientific and pharmaceutical history of CCR5, discusses the world of intellectual property, and ends with thought-provoking final chapters that show where the author's heart lies as he invites his audience to reconsider some assumptions and unite with historians and anthropologists before diving into the world of "racial" and "ethnic" descriptions to distinguish populations. Each of the subjects is given scholarly treatment with an exceptional number of notes to chapters and references.

The late Jonathan Mann once stated that the earliest years of HIV/AIDS research saw the fastest advances in medical history from the onset of a new disease. In 4 years, U.S. clinicians first described the disease, CDC defined the risk factors, the virus was linked to AIDS, the blood test was developed, the target cells identified, the genome of HIV sequenced, most genes and proteins determined, early mechanisms of pathogenesis elucidated, HIV variation discovered, the beginning of systemic therapy for a viral disease initiated, and reagents made available worldwide. Almost rivaling those beginning years of HIV/AIDS research, another period (1995–1996) includes the development of combination anti-HIV drugs that changed a horror story to a treatable chronic disease and another extraordinary advance which gave rise to this book: finding the HIV co-receptor, which on first thought would not appear to be such a milestone as to provide Jackson a book opportunity.

The story begins with evidence that more than CD4 was needed for HIV to enter cells, followed by the finding that β chemokines, known ligands for CCR5, were powerful blockers of HIV infection. It was quickly shown that CCR5 was indeed a critical co-receptor for HIV. Soon the famous CCR5-Δ32 mutant resulting in a disabled protein unable even to reach the cell membrane was discovered. The consequence is a slowing of progression to AIDS in an already infected person heterogeneous for the mutant gene, and in some cases of homogenous CCR5-Δ32 mutations, complete protection against infection from HIV. When a strikingly greater prevalence was found in northern Europeans, race and ethnicity became a subject of interest. So began a search for the origin of the presumed selective pressure that gave rise to CCR5-Δ32 and a number of false hypotheses beginning with the Black Death plague of the 14th century and the assumption that some advantage came by way of Δ32. This was presented with fanfare in general media, but it was soon discovered that the mutations were of similar frequency in people who died of plague versus those who died from famine. The theory was slowly eliminated



to be picked up by a small pox hypothesis, though by this time the International Haplotype Map was showing no evidence of any selection for CCR5-Δ32 unless it was over 1,000 years ago, leading to the suggestion that the organism responsible for CCR5-Δ32 was likely a filovirus causing hemorrhagic fever, such as Ebola, and dispersed by Vikings. More recently, a 2,000 year history has been more convincingly argued, with the virus becoming more prevalent in the early renaissance because of sporadic epidemics of these hemorrhagic viruses, and suggesting the ancient Romans dispersed it. It is important to note that these hypotheses are based on very limited data and rely on history and mathematical modeling except one—the recent discovery that CCR5-deficient mice resist *Staphylococcus aureus* infection, providing the first laboratory result suggestive of a mechanism. The story is yet unsettled, but it provides Jackson the first of his several pleas for new cooperation between scientists, anthropologists, and historians.

Companies soon entered the field envisioning therapeutic strategies by discovering molecules that bind to CCR5 and a diagnostic for CCR5-Δ32 for determining (1) if one was less likely to be infected; (2) if infected, predicting progression at a slower rate; or (3) for identification of CCR5-Δ32 people whose bone marrow could be used for transplanting HIV-resistant cells to an HIV infected person as was carried out in the one suspected HIV cure—the so-called Berlin patient, although this a dangerous and generally impractical approach. Thus began an intensification of biotech and pharmaceutical competition over intellectual property and patent validity and the entry of "race" and "ethnicity" into the story. Pfizer utilized a modern approach of screening by a receptor binding assay to identify Maraviroc as its lead entry blocker. From the pioneering studies that led to AZT and subsequent development of a host of other RT inhibitors by a number of companies—culminating in the so-called cocktail of HIV protease inhibitors and RT inhibitors. Still more inhibitors were brought forward, and it is in the latter part of these developments that Maraviroc made its debut. Since so many drugs are needed because of side effects

and drug resistance, Maraviroc was introduced because its mode of action was novel, its tolerance excellent, and its capacity to reduce HIV high. Yet today it remains reserved for drug-resistant patients likely because of its cost, although India produces the generic version at a lower price. The question is raised, but never answered, regarding how much it cost the industry to develop this drug. The unsolved problem is what is a fair price and how can the more expensive drugs be made available to all? Clearly this requires government intervention.

But the position of Jackson's heart is never in doubt. Nowhere is this more evident than the first discussion of gene patenting—the story of Human Genome Science (HGS) and its founder, William Haseltine. HGS succeeded in obtaining a patent for virtually all uses of chemokine receptors discovered in the future, though having only a partial gene sequence that had some homology to known sequences of chemokine receptors, but no actual identity or function, let alone disease association and medical use of the approved sequence. Shortly after the HGS patent, work from academia in search of the HIV co-receptor made the essential discoveries related to CCR5, including its practical uses. I find the HGS patent on CCR5 analogous to a man who finds and stores a piece of onyx. Someone else soon discovers the same and demonstrates that it has several uses by its sharpness that is unrecognized by the "picker," who is able to control all future use of onyx. Whereas it is possible to understand complexities facing the U.S. patent office, it is impossible to agree with their original decision. Jackson then presents his case against the wide use of patents especially by scientists in academia by using history (German chemistry) and several other enlightening stories. However, I am not convinced by Jackson in two arguments: his generalization from discussions with some scientists who stated that it was competitive recognition of discovery that gave them their drive and not the desirability of patents, and second, that because the U.S. government provides substantial research funding there is little need for academics to favor relationships with companies that provide funding. In the former, I find scientists vary greatly with respect to their interest in patents as a helpful motivator. As to the latter, most biomedical scientists today are keenly aware of the relative decline in NIH available funding, and I suspect a significant percent favor funding from pharmaceutical or biotech industries, especially when the "price" is right, the relationship not overdone, and all of it well monitored.

Another view from Jackson's window shows the potential for use of genomics and development of drugs that are race directed and even challenges us to define race and our avoidance of other parameters for genealogy studies instead of race. He notes that drugs that appear to work better with certain races sometimes "save" a drug that failed in an earlier study of the general population. The approach also appeals to the current cry for precision medicine and even to racial communities seeking greater medical focus on their needs. Jackson points out that in some instances, these claims have been based on shady results. For me, these discussions were eye-openers and suggest deeper thought is needed by those of us in biomedical research when we draw race-related inferences from genomics or think we are on the right track when we select drugs for different races predicated on so-called precision medicine.

Though not stated as such, the author has recommendations throughout the book. They include: (1) The need for interactions of molecular geneticists with other field leaders especially historians and anthropologists; (2) precise definitions of race and ethnicity prior to their use in genomic studies; (3) using parameters other than race in comparative genetic studies, e.g., geography, climate, population histories; (4) a continued debate on what is patentable; (5) greater consideration of the negative impacts of patents on science progress and affordability of available drugs; and (6) a rethinking of the financial need for academics relying on industry for financial support.

Jackson's epilogue closes with his statement that the book "has gestured at the role of history in public policy … told the tale of historical alternatives" with an attempt to "resurrect the past to illustrate the paths not taken" and the reason why. He notes, "Histories that feature only the victors and that forget that objects can be exploited by those in power with sinister results." This is a poignant ending but the book is more. It is also an exceptionally well-documented analysis of the intricacies and dilemmas of modern biomedical science through the window of a gene—intimately involved in the outcome of one of the greatest pandemics of modern times.

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